Treatment Guidelines for Rheumatologic Manifestations of Sjögren’s: Use of Biologics, Management of Fatigue and Inflammatory Musculoskeletal Pain

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Significance and Innovation:

- First description of US clinical practice guidelines for primary Sjögren’s syndrome
- Includes recommendations for the use of biologic agents, and management of fatigue and inflammatory musculoskeletal pain
Abstract

Objective: The Sjögren’s Syndrome Foundation (SSF) Clinical Practice Guidelines (CPG) are designed to improve quality and consistency of care in Sjögren’s by offering recommendations for management.

Methods:
Management questions for the systemic manifestations of Sjögren’s were posed by the CPG committee (CPGC) with input from patients and rheumatologists. Clinical questions were assigned to a topic review group (TRG) which performed systematic reviews, data extraction and drafted guidelines. Quality of evidence and strength of recommendation were rated using ASCO’s modification of GRADE. Guideline recommendations were reviewed by a consensus expert panel (CEP) comprised of 30-40 clinicians from academia and community practices as well as RNs and patients using a modified Delphi process. A CEP agreement level of 75% was set as a minimum for adoption of a guideline recommendation.
Results: Consensus was achieved for 19 recommendations; for 11 additional modules, available data was insufficient to allow a recommendation to be formulated. Of the 18 recommendations, 14 required 1 Delphi round, 3 required 2 and 1 required 3.

Conclusions: Key recommendations include: A decision tree for the use of oral DMARDs for inflammatory musculoskeletal (MSK) pain; use of self-care measures and advice regarding exercise to reduce fatigue; and the use of rituximab in selected clinical settings for oral and ocular dryness and for certain extraglandular manifestations, including vasculitis, severe parotid swelling, inflammatory arthritis, pulmonary disease and mononeuritis multiplex. The CPGC strongly discouraged the use of TNFα inhibitors for sicca symptoms and for the majority of clinical contexts in primary Sjögren’s.
Sjögren’s syndrome remains under-recognized despite being a highly prevalent autoimmune rheumatic disorder that affects up to 3.1 million Americans (1). The prevalence doubles when including those with an additional connective tissue disease. The disease is associated with a high burden of illness, diminished quality of life (2, 3, 4) and increased healthcare costs (5, 6, 7). Sjögren’s is also associated with an increased relative risk of developing non-Hodgkin B cell lymphoma (8). Clinical Practice Guidelines (CPG) were developed by the Sjögren’s Syndrome Foundation (SSF) in response to patient requests for improved care and physician requests for guidance.

The primary goal of the SSF initiative was to improve the quality and value of care in Sjögren’s by developing CPG for the assessment and management of systemic manifestations, dry eyes, dry mouth and, to create a guidance document for U.S. clinicians. The secondary goal was to obtain broad awareness of these guidelines by key stakeholders including key professional and government organizations as well as healthcare insurance entities. The SSF determined key guiding principles at the start of the process, including participation of key stakeholders, transparency, and consistency. The SSF funded and staffed conferences for the CPG initiative and co-partnered with the ACR Quality of Care Committee and staff which provided guidance throughout this process. The Foundation appointed a Chair who then, in conjunction with the SSF, appointed six Co-Chairs for three Working Groups to cover Rheumatology/Systemic disease, Ocular, and Oral manifestations. The current manuscript addresses the rheumatologic topics. All Working Groups followed common processes and a specific order of tasks to reduce bias as much as possible. For the purpose of these CPG, the
Chairs and Working Group members addressed treatment questions among those Sjögren’s patients without a second major rheumatic/autoimmune disease (or “primary” Sjögren’s as it traditionally has been referred). While guideline recommendations provide a rational approach to various management issues, clinicians will ultimately utilize their best clinical judgment in practice. A degree of inherent bias is unavoidable but reduced as much as possible through the use of a rigorous and transparent process, the low percentage of potential conflicts of interest by participants as guided by ACR policies (9), and the use of an external consensus panel that voted and commented on the recommendations as they were finalized.

The guidelines provide evidence-based recommendations whenever possible and expert opinion when insufficient evidence exists. These first ever standard of care guidelines for systemic Sjögren’s in the U.S. will improve consistency in practice patterns, inform coverage and reimbursement policies, lead to the design and implementation of needed educational programs, highlight areas for future research and, most importantly, fill a significant clinical void.

Methods

Principles

The SSF CPGC adopted the principles of AGREE, an international appraisal instrument for assessing guidelines quality (10, 11). One of the most important and overriding principles during the project was that physician and patient priorities be taken into consideration at the outset of this process. All key stakeholders, including patients, practicing and academic rheumatologists and the SSF as a patient advocacy organization, were included in the guidelines development initiative. Surveys of patient priorities were conducted during a SSF National Patient Conference and through use of SSF media (email, website, Facebook). In addition, patients were appointed to the CPGC and served on the CEPs. Opinions of practicing
rheumatologists were obtained during exit surveys at Sjögren’s “Meet the Professor” sessions held during an ACR annual scientific meeting.

**Work Process**

Initially, 97 potential topics for guideline development were identified by review of stakeholder surveys. After further face-to-face and e-mail discussions, the list was narrowed to 16 topics (see the online supplementary materials) Appendix 1 Table 1 that were ranked by vote of the working group. Significance was rated on a 1-5 Likert scale (1 = possibly important to some, important to some, important, very important to all, crucial to all stakeholders = 5). A score of ≥4.0 was established as a cut-off for guideline development. Topics were expressed as clinical questions. This manuscript reports on the following three questions: 1) Are non-biologic DMARDs (Disease Modifying Anti-rheumatic Drugs) useful for the treatment of inflammatory musculoskeletal (MSK) pain; 2) Are biologics effective and safe in management of sicca and systemic manifestations; and 3) Are there effective management strategies for fatigue? Each topic question was assigned to a Topic Review Group (TRG) composed of members from specialties relevant to that topic question. The “Musculoskeletal TRG” included three rheumatologists; the “Biologic TRG” included two rheumatologists, two oral medicine specialists and an ophthalmologist; and the “Fatigue TRG” included 3 rheumatologists. An expert methodologist was recruited to guide the entire process.

**Search Strategy**

The systematic review of the literature was conducted with the assistance of a librarian using MEDLINE/PubMed and the Cochrane database to search for peer-reviewed articles published in English between January 1, 1988 and April 13, 2015. Literature search results for each topic are summarized by the quorum diagrams (Fig 1-3). Individual search strategies, inclusion parameters and search terms are provided in supplementary materials. Subjects of included articles were allowed to meet any published Sjögren’s classification criteria. Subjects
may have had concurrent non-Hodgkin’s lymphoma, but intervention studies must have been primarily designed to measure outcomes related to primary Sjögren’s. Acceptable endpoint measures were decided \textit{a priori} by TRG consensus and used to build worksheets for data extraction. Studies reviewed included: meta-analyses, systematic reviews, randomized controlled trials (RCTs) as well as prospective case studies and series where outcomes for treatment were prospectively defined. Minimum treatment follow-up interval was defined as 12 weeks. Systematic reviews were utilized to ensure capture of references and provide a contextual overview for the TRG.

**Quality of Evidence and Strength of Recommendation**

As presented in the Data Extraction Tables and Templates 1 and 2 in the supplementary materials, 11 parameters were used to assess evidence quality. These resulted in an overall quality rating for each study. Standardized rating scales according to GRADE methodology were utilized to assess quality of evidence (rated as “high”, “moderate”, “low”, “very low”) for individual studies and the overall body of evidence for each topic (12). The rating for the overall quality of evidence was the lowest quality rating among the outcomes critical for comparison between interventions. In the absence of any data, the quality of evidence was rated as “very low” as were all recommendations based on case reports, case series and expert opinion.

The strength of recommendation was rated as “strong”, “moderate” or “weak” according to the American Society of Clinical Oncology (ASCO) modification of GRADE (13). The ASCO rating scale and terms used for strength of recommendation can be found in supplementary materials. Appendix 1, Table 2
Guidelines Development

Two members of each TRG independently extracted data from selected manuscripts. The guideline protocol worksheet and data extraction tables are available in the supplementary materials. Studies meeting inclusion/exclusion criteria as developed by each TRG were extracted to record study characteristics, study population, evidence and to assess the quality of evidence for each included study. The Data Extraction Table for Quality in the supplementary materials and the “Guideline Protocol Worksheet Template” display the 11 parameters used to assess evidence quality, including an overall quality rating for each study. A draft of each guideline recommendation and strength of recommendation accompanied by a clinical rationale, literature review outline, evidence tables and evidence summary was then sent electronically to the CEP for voting. Each CEP was comprised of 33-41 members with expertise aligned to the particular guideline topic. Each CEP included practitioners and patients. Achievement of 75% agreement was required to approve a guideline recommendation. All CEP comments and agreement percentages were reviewed by the TRG and draft guidelines revised as necessary and sent back to the CEP for re-voting (supplementary material Fig.1) until the minimum percent agreement was reached. The maximum number of voting rounds required to achieve consensus was three. If consensus was not achieved after three rounds, no recommendation was issued.

Disclosures and Management of Conflicts of Interest

All participants signed ACR conflict of interest forms, and disclosures and/or conflicts of interest were managed in accordance with ACR policy. Conflict of interest statements were revised and reviewed for each working group member on a periodic basis. A conflict of interest was identified if any
participant had any relationship with an affected company regardless of the relationship type. No conflicts were identified in the majority (>51%) of all guideline development team members for the duration of the project. The overall CPG Chair (project PI) and TRG leaders had no relevant conflicts of interest during the project. The CPG Chair was not permitted to vote on any recommendation. Additionally, the TRG leaders were not permitted to vote as members of the CEP on any recommendations they drafted.

For more detailed information on the Sjögren’s CPG development process including: priority topics, clinical questions, literature reviews, clinical rationales, evidence tables, evidence summaries, additional references, and suggestions for future studies please see the supplementary materials.

RESULTS

Biologic Therapy for Sicca and Systemic Manifestations of Sjögren’s (Table 1)

After consideration of each literature review, clinical rationale, evidence summary and recommendation, the Clinical Practice Guidelines Consensus Panels completed a modified Delphi exercise and reached agreement (e.g. > 75% consensus) on the following recommendations:

**TNF-α Inhibitors:** TNF-α inhibitors **SHOULD NOT BE USED** to treat sicca symptoms in patients with primary Sjögren’s. This recommendation is based on a small controlled trial (14) and a multicenter RCT (15). If TNF-α inhibition therapy is used for RA or other related overlap conditions in Sjögren’s patients, health care providers should consider and monitor for toxicities listed in Table 1. Despite theoretical concerns regarding lymphoma in Sjögren’s, there is no evidence that the subset of RA patients with Sjögren’s who have been treated with anti-TNF-α agents have an increased incidence of lymphoma. Therefore, this recommendation should not be interpreted to discourage use of TNF inhibitors in situations where there is overlap with RA or where TNFα inhibition therapy is indicated for the treatment of inflammatory arthritis.

**Rituximab:** Rituximab **MAY BE CONSIDERED** as a therapeutic option for keratoconjunctivitis sicca (KCS) in patients with primary Sjögren’s and for whom conventional therapies, including
topical moisturizers, secretagogues, anti-inflammatory agents, immunomodulators and punctual occlusion, have proven insufficient. **Rituximab MAY BE CONSIDERED** as a therapeutic option for xerostomia in patients with primary Sjögren’s with some evidence of residual salivary production, significant evidence of oral damage as determined by the clinician, and for whom conventional therapies, including topical moisturizers and secretagogues, have proven insufficient. Although a recent RCT did not meet a composite of primary endpoints (pain, fatigue, sicca and global improvement), these recommendations are based on data from analysis of secondary outcome measures (16) and a smaller RCT (17). **Rituximab MAY BE CONSIDERED** as a therapeutic option for adults with primary Sjögren’s and any or all of the following systemic manifestations: vasculitis, with or without cryoglobulinemia, severe parotid swelling, inflammatory arthritis, pulmonary disease and peripheral neuropathy; especially mononeuritis multiplex. This recommendation is based on a non-randomized comparator trial (18) and case reports and series which reported on end-organ outcomes for a total of 175 patients as well as registry studies (19, 20). It is also based on extrapolation of the use of rituximab in other rheumatologic conditions including RA and vasculitis. Overall, the quality of evidence was “low”, and the “moderate” strength of recommendation was based on expert opinion with CEP agreement reaching 97% for this recommendation. Significant risks may be associated with the use of rituximab and clinicians should exercise caution and monitor Sjögren’s patients closely for the toxicities listed in Table 1.

**Guideline Recommendations for the Management of Fatigue in Sjögren’s (Table 2)**

**Self-care measures:** Education about self-care measures **SHOULD** include advice about exercise to reduce fatigue in Sjögren’s. These measures have been demonstrated to reduce fatigue in RA (21), SLE (22,23,24) and MS (25) as well as in one small RCT in Sjögren’s (26). **Hydroxychloroquine:** Hydroxychloroquine **MAY BE CONSIDERED** in selected situations to treat fatigue in Sjögren’s. This approach is largely based on experience in patients with systemic
lupus and a 1996 uncontrolled, retrospective study (27) that reported improvement of fatigue in roughly 1/3 of Sjögren’s patients treated with hydroxychloroquine. This study evaluated patients with an elevated ESR or other extraglandular manifestations (e.g. arthralgias, rash, and lymphadenopathy). A subsequent RCT failed to verify this initial observation but was of relatively short duration (28). Nonetheless, comments from the CEP from rounds 1 and 2 demonstrated strong support for maintaining an option for use of HCQ for fatigue. A change of recommendation from the former statement: “HCQ should not be used for fatigue” to the current recommendation that “HCQ may be considered in selected situations to treat fatigue” resulted in a nearly 30% increase in agreement in the Delphi consensus process. Although quality of the overall body of evidence was rated as “very low”, the CEP members cited clinical experience with HCQ and a favorable safety profile in this setting as reasons for considering HCQ in Sjögren’s patients with fatigue.

**DHEA:** DHEA is **NOT RECOMMENDED** for treatment of fatigue in Sjögren’s. This is based on two well-designed RCTs in Sjögren’s patients showing no difference between DHEA and placebo (29, 30).

**TNF-α inhibitors:** Neither etanercept nor infliximab is recommended for treatment of fatigue in Sjögren’s (14, 15).

**Newer biologics:** The TRG concluded that insufficient data and/or clinical experience exists to make a recommendation regarding the use of anakinra (31), abatacept (32), belimumab (33) and epratuzumab (34) for fatigue in Sjögren’s.

**Guideline Recommendations for the Use of DMARDS for Inflammatory Musculoskeletal Pain (Table 3)**

The recommendation for the use of DMARDs for inflammatory MSK pain is presented as a decision tree. Inflammatory musculoskeletal pain largely comprises symptoms related to non-erosive
synovitis, polyarthritis, and inflammatory myositis. The first line treatment for inflammatory MSK pain in primary Sjögren’s should be hydroxychloroquine (HCQ). While a recent RCT (28) did not meet the endpoint for pain, the moderate strength of recommendation and 92% agreement of the CEP is based on the significant reported improvement in inflammatory markers following use of HCQ (27,28,35,36), improvement of MSK pain in other studies (27,35,37) and the favorable safety profile of HCQ compared to other DMARDs. If hydroxychloroquine is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, methotrexate alone may be considered. This recommendation received 88% agreement from the CEP and was based on extrapolation from long-term experience in RA and SLE as well as two studies in Sjögren’s (37, 38). Quality rating for the overall body of evidence for recommendations #1-2 was “low” and was “very low” for the remaining recommendations.

If either hydroxychloroquine or methotrexate alone is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, hydroxychloroquine plus methotrexate may be considered. If hydroxychloroquine plus methotrexate is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, short-term (1 month or less) corticosteroids of <=15mg a day may be considered (96% agreement). Long-term (more than 1 month) ≥15mg a day corticosteroids may be useful in the management of inflammatory musculoskeletal pain in primary Sjögren’s, but efforts should be made to find a steroid-sparing agent as soon as possible. If hydroxychloroquine and/or methotrexate or short-term (1 month or less) corticosteroids are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, leflunomide may be considered. If hydroxychloroquine and/or methotrexate, corticosteroids, or leflunomide are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, sulfasalazine may be considered. If hydroxychloroquine and/or methotrexate, corticosteroids, leflunomide, or sulfasalazine are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, azathioprine may be considered. There was strong agreement (92%) among the CEP
that if major organ involvement occurs in the primary Sjögren’s patient, **azathioprine** would be a better choice than leflunomide or sulfasalazine for the treatment of all extraglandular manifestations including inflammatory musculoskeletal pain. If none of the above agents are effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, **cyclosporine** may be considered.

**DISCUSSION**

Among all chronic autoimmune rheumatic disorders, Sjögren’s remains one of the most difficult to manage. Development of clinical practice guidelines for the ocular (39), oral (40) and systemic/rheumatologic manifestations should substantially improve the quality and consistency of care, guide reimbursement policies, and decrease the overall burden of illness. At the present time, no curative or “remittive agent” exists. Thus, therapeutic goals remain symptom palliation, improved quality of life, prevention of damage, and appropriate selection of patients for immunosuppressive therapy.

Several obstacles made the assessment of studies and the overall guidelines development process challenging including the changing disease definitions and/or classification criteria for Sjögren’s over time, a relative paucity of large randomized clinical trials, changing outcome measures, and the large number of null trials. It was therefore decided *a priori* that to be included for data extraction, a study was required to meet any published Sjögren’s classification criteria set. A list of “acceptable” outcome measures for each organ system was defined by the relevant TRG prior to data abstraction. Even with the above measures instituted, a lack of consistent high quality evidence in the medical literature necessitated use of a modified Delphi process.

The analysis of Sjögrens trial data revealed many important observations. First there is no standard for clinically meaningful improvement. It is also difficult to distinguish between
disease activity and damage and, therefore, challenging to identify active cases to achieve a meaningful response. The heterogeneity of the disease group also makes it difficult to recruit patient populations to study single primary endpoints. Therefore, the composite indices or multiple parameters that are usually studied simultaneously to circumvent this problem also inherently limit the power of the study. Until recently, none of the composite outcome measures in use except for ESSDAI (EULAR Sjögren’s Syndrome Disease Activity Index) (41) and ESSPRI (EULAR Sjögren’s Syndrome Patient Reported Index) (42) have been validated. Future, use of these, as well as others in development (e.g. SSRI, Sjögren’s Syndrome Responder Index) (43) coupled with discovery of novel biomarkers will help to resolve these issues.

**Biologic Therapy in Sjögren’s Disease**

For the majority of patients with Sjögren’s, the burdens of cost and potential side effects of biologic therapy, at the present time, still outweigh the potential benefits as demonstrated by the evidence. Among the available biologics studied in Sjögren’s to date, some evidence exists that rituximab has benefits for certain extraglandular manifestations and sicca signs and symptoms (17). The guidelines recommend this treatment approach for Sjögren’s patients with internal organ or systemic involvement but only those individuals who have already failed DMARDS and/or corticosteroids due to lack of efficacy or unacceptable toxicity. Similarly, the decision to use a biologic such as rituximab to treat dry eyes and/or dry mouth would only be appropriate in severe cases and with the necessary input from the patient’s ocular and/or oral medicine specialist. The recommendation for possible use of rituximab for keratoconjunctivitis sicca parallels a similar recommendation made independently by the SSF Ophthalmology CPG. (39) Yet since the full degree of therapeutic benefit remains unclear, this option is only recommended after careful consideration of the risk/benefit ratio. Therefore the strength of this recommendation was rated as “weak”.
Recently, the largest controlled trial of rituximab to date (TEARS trial) failed to meet a composite of primary endpoints at 6 months (44). However, a statistically significant benefit vs. placebo was noted for certain individual parameters (e.g. fatigue, sicca, global improvement) at the 6 month interval and/or other time points. TEARS highlights the key issues in Sjögren’s trial design, patient selection, outcome measures and biologic treatment regimens noted above. Recently, Cornec et al (43), derived a Sjögren’s syndrome responder index (SSRI) using positive endpoints from TEARS. The SSRI quantitated the proportion of subjects demonstrating ≥ 30% improvement in 2 of 5 of VAS for ocular dryness, oral dryness and fatigue as well as UWSF and ESR. In this post-hoc analysis, a statistically significant improvement in the SSRI was observed in the rituximab-treated subjects vs. placebo.

Evidence from a limited number of studies suggest that TNF-α inhibitors do not ameliorate sicca symptoms or other manifestations in established Sjögren’s (14,15,45). However, it is not currently known whether this conclusion would change if clinical trials were conducted in very early disease. In addition, the consensus expert panel emphasized that the proposed guideline recommendations do not preclude the use of TNF alpha inhibitors in Sjögren’s patients with overlapping features of rheumatoid arthritis or in situations where TNF-α inhibition is otherwise indicated for the treatment of another inflammatory illness.

Management of Fatigue

Fatigue remains one of the most difficult management dilemmas in Sjögren’s (46). The CPGC emphasized that causes of fatigue in Sjögren’s are numerous therefore necessitating a comprehensive diagnostic evaluation. Currently, the only strong therapeutic recommendation for fatigue in Sjögren’s is exercise (47). This provides the same benefit as seen for patients in other rheumatic disease groups.

Among pharmacologic therapies, hydroxychloroquine remains the most widely prescribed treatment in the United States to manage fatigue in Sjögren’s. This practice is largely
based on results of uncontrolled studies and clinical experience, since evidence of benefit in placebo controlled trials is lacking. Thus, the rating for quality of the overall body of evidence was “very low” and the strength of the recommendation was “weak”. Nevertheless, the panel felt that additional studies with different patient selection parameters, longer duration of therapy and alternate outcome measures are needed before concluding that use of hydroxychloroquine should be precluded in this setting.

DMARDs for Inflammatory Musculoskeletal Pain

The spectrum of inflammatory musculoskeletal pain in Sjögren’s patients ranges from mild arthralgias and myalgias to frank synovitis with chronic pain. (48) In devising a treatment algorithm for this indication, the TRG adopted a sequential approach. Recommendations for agents deemed to have similar efficacy and safety profiles, were grouped together in order to allow the clinician to choose a particular treatment based on his or her clinical experience and the circumstances of the individual patient. The TRG was unable to find high-quality evidence to support the use of DMARDs for this indication and therefore labeled the quality of evidence for each DMARD guideline as “low” or “very low” depending on the agent. Thus, recommendations were formulated largely based on expert opinion as guided by a modified Delphi consensus process. In certain instances, however, the strength of a recommendation was ultimately rated as “moderate” or “strong” because the TRG and CEP both agreed with a moderate to high level of confidence that the guideline recommendation reflected best current practice.

Although hydroxychloroquine remains the first line therapy for inflammatory musculoskeletal pain in Sjögren’s, clinicians may choose other DMARDS in certain situations or in more severe cases where the perceived benefits outweigh the risk of increased toxicity. These clinical scenarios include: 1) HCQ responsive patients who must discontinue this therapy due to toxicity or an adverse effect; 2) patients with an inadequate response to HCQ; 3)
patients with severe steroid responsive musculoskeletal pain and persistent symptoms who require another DMARD for steroid-sparing effect; and 4) patients with objective evidence of synovitis.

In summary, Sjögren’s remains a highly prevalent chronic autoimmune rheumatic disease with many unmet clinical needs. Clinical practice guidelines were developed for the oral (40), ocular (39) and rheumatologic/systemic manifestations of Sjögren’s to inform clinicians’ management of patients in the U.S. population. In addition, this process has defined the need for future study in many areas (see Future Directions for Research in supplementary materials) including new outcome measures, targeted therapies for disease-specific manifestations and the development of novel biomarkers to identify “early” or treatment-responsive patients for participation in clinical trials. Guidelines will be revised as new studies are published.

References:


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24. Carvalho MR, Sato EI, Tebexreni AS, Heidecher RT, Schenkman S, Neto TL. Effects of supervised cardiovascular training program on exercise tolerance, aerobic capacity, and


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have participated to-date, including guideline methodologists, rheumatologists, nurses, other professional specialists who were included as needed, and Sjögren’s patients and the university librarians experienced in literature searches for guidelines who contributed to this initiative. The authors would like to thank Dr. Barbara Segal for her contributions to the Fatigue Topic Review Group. We are grateful to Patricia Hurley, MSc, as our methodology consultant and to Dr. Holger Schünemann for his expert advice regarding GRADE methodology. The authors would like to acknowledge the invaluable contributions of Dr. Elaine Alexander (deceased). We wish to acknowledge Ms. Debra Famigletti for assistance in preparation of the manuscript.
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**Fatigue**

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**DMARDs and Inflammatory Musculoskeletal Pain**

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The following served on at least one consensus expert panel for the Recommendations in this paper, and many served on all of the panels.

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13. Theresa Lawrence Ford, MD, FACR, North Georgia Rheumatology Group, Lawrenceville, GA
14. Joseph Forstot, MD, FACP, FACR, Rheumatology Associates-S FI, Boca Raton, FL
15. Robert Fox, MD, PhD, FACR, FACR, Rheumatology Clinic, La Jolla, CA
16. Paul Howard, MD, MACP, FACR, Arthritis Health, Scottsdale, AZ
17. Judith James, MD, FACR, Arthritis & Clinical Immunology Oklahoma Medical Research Foundation, Oklahoma City, OK
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19. Stuart Kassan, MD, FACR, FACR, MACR, Colorado Arthritis Associates, Lakewood, CO and University of Colorado, Denver, CO
20. Janet E. Lewis, MD, FACR, University of Virginia, Charlottesville, VA
21. Arthur Mandelin, MD, PhD, FACR, McGaw Medical Center, Northwestern University, Chicago, IL
22. Timothy Niewold, MD, FACR, Mayo Clinic, Rochester, MN
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30. Bruce Rothschild, MD, FACR, Rheumatology Human Motion Institute, Indiana, PA
31. Nora Sandorfi, MD, Hospital of the University of Pennsylvania, Philadelphia, PA
32. R. Hal Scofield, MD, FACR, Oklahoma Medical Research Foundation, University of Oklahoma Health Sciences Center, and Department of Veterans Affairs Medical Center, Oklahoma City, OK
33. Daniel Small, MD, FACR, Sjögren’s Center of Florida, Sarasota Arthritis Center, Sarasota, FL
34. Harry Spiera, MD, MACR, Rheumatology Associates, New York, NY
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3. Troy Daniels, DDS, MS, UCSF School of Dentistry, San Francisco, CA
4. Andres Pinto, DMD, MPH, Case Western Reserve University, Cleveland, OH
5. James Scuibba, DMD, PhD, Greater Baltimore Medical Center, Baltimore, MD
6. Carol M. Stewart, DDS, UF Health, University of Florida Health Science Center, Keystone Heights, FL

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2. S. Lance Forstot, MD, FACS, Corneal Consultants of Colorado, Denver, CO
3. Gary Foulks, MD, FACS, University of Louisville School of Medicine, Louisville, KY
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2. Fred Friedberg, PhD, Stony Brook University, Stony Brook, NY
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4. Steven Mandel, MD, PC, Neurology Private Practice, New York, NY
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7. Lynn Petrucci, RN, MSN, Formerly, West Shore Surgery Center, Mechanicsburg, PA**
8. Sarah Schafer, MD, Public Health and General Preventive Medicine, Oakland, CA**
9. Nancy Schoofs, RN, PhD, Grand Valley State University, Grand Rapids, MI**

*Oral and Ocular members participated in the Biological Therapy-Sicca Symptoms guidelines only, with the exception of the first name under Oral experts.** Sjögren’s patient
Table 1

Recommendations from the Biologic TRG

<table>
<thead>
<tr>
<th>Recommendation #1 - TNF-α Inhibitors</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α inhibitors SHOULD NOT BE USED to treat sicca symptoms in patients with primary Sjögren’s.*</td>
<td>STRONG</td>
</tr>
</tbody>
</table>

*Note that this recommendation should not be interpreted to discourage use of TNF-α inhibitors in situations where there is overlap of Sjögren’s with rheumatoid arthritis (RA) or other conditions where TNF-α inhibition therapy is indicated for the treatment of inflammatory arthritis.

Percent agreement – 100 – Round 1

<table>
<thead>
<tr>
<th>Recommendation #2 - TNF-α Inhibitor Cautions</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>If TNF-α inhibition therapy is used for RA or other related overlap conditions in Sjögren’s patients, health care providers should consider and monitor for the following:*</td>
<td>STRONG</td>
</tr>
</tbody>
</table>

* Lymphoma and other malignancies; health care providers should be cognizant that patients with primary Sjögren’s have an increased risk of non-Hodgkin’s lymphoma as compared to the general population
  - Serious infections, including tuberculosis
  - Invasive fungal infections
  - Hepatitis B reactivation
  - Hepatotoxicity
  - Heart failure
  - Cytopenias
  - Hypersensitivity; Serious infusion reactions
  - Demyelinating disease

*Patients and physicians should refer to the FDA label for additional information

Percent agreement - 100 – Round 1

<table>
<thead>
<tr>
<th>Recommendation #3 – Rituximab for KCS</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab MAY BE CONSIDERED as a therapeutic option for keratoconjunctivitis sicca (KCS) in patients with primary Sjögren’s and for whom conventional therapies, including topical moisturizers, secretagogues, anti-inflammatory, immunomodulators and punctual occlusion, have proven</td>
<td>WEAK</td>
</tr>
</tbody>
</table>
Recommendation #4 – Rituximab for Xerostomia

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab MAY BE CONSIDERED as a therapeutic option for xerostomia in patients with primary Sjögren’s with some evidence of residual salivary production, significant evidence of oral damage as determined by the clinician, and for whom conventional therapies, including topical moisturizers and secretagogues, have proven insufficient.</td>
</tr>
</tbody>
</table>

Percent agreement – 87.1 – Round 3

Recommendation #5 – Rituximab for Systemic Symptoms

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab MAY BE CONSIDERED as a therapeutic option for adults with primary Sjögren’s* and any or all of the following systemic manifestations: ● Cryoglobulinemia associated with vasculitis ● Vasculitis ● Severe parotid swelling ● Inflammatory arthritis ● Pulmonary disease ● Peripheral neuropathy – especially mononeuritis</td>
</tr>
</tbody>
</table>

*Note: These patients should have had a suboptimal response to standard oral DMARD agents and/or have experienced unacceptable toxicity from these agents or corticosteroids or are incapable of tapering and discontinuing corticosteroids.

Percent agreement – 96.9 – Round 2

Recommendation #6 – Rituximab Cautions

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients and health care providers should be aware that, although uncommon, significant harms may be associated with the use of rituximab and should exercise caution and observe for the following when using rituximab in Sjögren’s patients:*</td>
</tr>
</tbody>
</table>

- Infusion reactions
- Tumor lysis syndrome in those with NHL
- Progressive multifocal leukoencephalopathy (PML)
- Hepatitis B reactivation with possible fulminant hepatitis
- Severe mucocutaneous reactions
- Infections
- Bowel obstruction and perforation
- Cardiac arrhythmias and angina
- Cytopenias
- Serious bacterial, viral or fungal infections
- In pregnancy and nursing, the risk vs benefit must be carefully considered
- Health care providers should avoid giving live vaccines when patients are on rituximab.

*Patients and physicians should refer to the FDA label for additional information.

Percent agreement - 100 - Round 1
Table 2

Recommendations from the Fatigue TRG

<table>
<thead>
<tr>
<th>Recommendation #1 - Exercise</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education about self care measures SHOULD include advice about exercise to reduce fatigue in Sjögren’s.</td>
<td>STRONG</td>
</tr>
<tr>
<td>Percent agreement – 100 – Round 1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation #2 - Dehydroepiandrosterone (DHEA)</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA is NOT RECOMMENDED for treatment of fatigue in Sjögren’s.</td>
<td>STRONG</td>
</tr>
<tr>
<td>Percent agreement – 90.2 – Round 1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation #3 – Hydroxychloroquine</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine MAY BE CONSIDERED in selected situations to treat fatigue in Sjögren’s.</td>
<td>WEAK</td>
</tr>
<tr>
<td>Percent agreement - 94.4 – Round 2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation #4 - TNF-α Inhibitors</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither Etanercept nor infliximab is recommended for treatment of fatigue in Sjögren’s.</td>
<td>STRONG</td>
</tr>
<tr>
<td>Percent agreement - 97.4 – Round 1</td>
<td></td>
</tr>
</tbody>
</table>
Table 3

Recommendations from the Inflammatory Musculoskeletal pain TRG

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation #1</strong> - Hydroxychloroquine (HCQ)</td>
<td><strong>MODERATE</strong></td>
</tr>
<tr>
<td>A first line of treatment for inflammatory musculoskeletal pain in primary Sjögren’s should be <strong>hydroxychloroquine</strong>.</td>
<td>Percent agreement - 94.4 – Round 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation #2 – Methotrexate (MTX)</th>
<th>Strength of Recommendation</th>
<th>Recommendation #3 – HCQ plus MTX</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>If hydroxychloroquine is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, <strong>methotrexate</strong> alone may be considered.</td>
<td><strong>MODERATE</strong></td>
<td>OR</td>
<td>If either hydroxychloroquine or methotrexate alone is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, <strong>hydroxychloroquine plus methotrexate</strong> may be considered.</td>
</tr>
<tr>
<td>Percent agreement - 91.6 – Round 1</td>
<td></td>
<td>Percent agreement – 88.9 – Round 1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation #4a – ST Corticosteroids</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>If hydroxychloroquine plus methotrexate is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, <strong>short-term (1 month or less) corticosteroids</strong> of &lt;=15mg a day may be considered.</td>
<td><strong>STRONG</strong></td>
</tr>
<tr>
<td>Percent agreement – 97.2 – Round 1</td>
<td></td>
</tr>
<tr>
<td>Recommendation #4b – LT Corticosteroids</td>
<td>Strength of Recommendation</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Long-term (more than 1 month) ≥15mg a day corticosteroids may be useful in the management of inflammatory musculoskeletal pain in primary Sjögren’s, but efforts should be made to find a steroid-sparing agent as soon as possible. Percent agreement -91.4 – Round 1</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
The following three recommendations are numbered in order of the Topic Review Group’s preference and experience. However, the TRG is grouping these together to allow the physician to choose any of the following and in any order based on that physician’s experience and the individual patient.

<table>
<thead>
<tr>
<th>Recommendation #5 - Leflunomide</th>
<th>Strength of Rec</th>
<th>Recommendation #6 - Sulfasalazine</th>
<th>Strength of Rec</th>
<th>Recommendation #7 – Azathioprine</th>
<th>Strength of Rec</th>
</tr>
</thead>
<tbody>
<tr>
<td>If hydroxychloroquine and/or methotrexate or short-term (1 month or less) corticosteroids are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, <strong>leflunomide</strong> may be considered.</td>
<td><strong>WEAK</strong></td>
<td>OR If hydroxychloroquine and/or methotrexate, corticosteroids, or leflunomide (Arava®) are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, <strong>sulfasalazine</strong> may be considered.</td>
<td><strong>WEAK</strong></td>
<td>OR If hydroxychloroquine and/or methotrexate, corticosteroids, leflunomide, or sulfasalazine are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, <strong>azathioprine</strong> may be considered.</td>
<td><strong>WEAK</strong></td>
</tr>
<tr>
<td>Percent agreement 80 – Round 1</td>
<td></td>
<td>Percent agreement 83.3 - Round 1</td>
<td></td>
<td>Percent agreement 86.1 – Round 1</td>
<td></td>
</tr>
</tbody>
</table>

**Recommendation #8 – Azathioprine**

If major organ involvement occurs in the primary Sjögren’s patient, **azathioprine** may be a better choice than leflunomide or sulfasalazine for the treatment of all extra glandular manifestations including inflammatory musculoskeletal pain.

Percent agreement – 91.7 – Round 1

**Recommendation #9 – Cyclosporine**

If hydroxychloroquine and/or methotrexate, corticosteroids, leflunomide, azathioprine, or sulfasalazine are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren’s, **cyclosporine** may be considered.*

* Few physicians have noted experience with cyclosporine in Sjögren’s, and many have stated a greater level of experience with and a preference for using a biologic in place of cyclosporine.

Percent agreement - 75.0 – Round 1
Figure 1

Quorum diagram for Biologic TRG

482 titles retrieved from search

115 abstracts reviewed

11 manuscripts met inclusion parameters for data extraction (sicca outcomes)

8 manuscripts met inclusion parameters for data extraction (systemic outcomes)

16 case reports/series met inclusion parameters for data extraction (systemic outcomes)
Figure 2

Quorum diagram for Fatigue TRG

475 titles retrieved from search

217 abstracts reviewed

19 manuscripts met inclusion parameters for data extraction
Figure 3

Quorum diagram for the Inflammatory MSK Pain TRG

- Search 1: 182 titles
- Search 2: 24 titles
- Search 3: 294 titles
- Search 4: 532 titles

1060 abstracts reviewed

10 manuscripts met inclusion parameters for data extraction